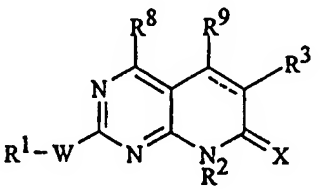
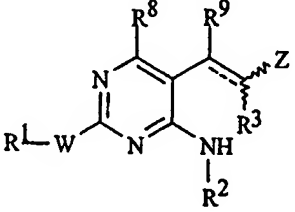


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<p>(21) International Application Number: PCT/US98/01343 (22) International Filing Date: 26 January 1998 (26.01.98) (30) Priority Data: 60/037,220 5 February 1997 (05.02.97) US 60/069,743 16 December 1997 (16.12.97) US (71) Applicant (for all designated States except US): WARNER LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BOSCHELLI, Diane, Harris [US/US]; 3A Elyse Drive, New City, NY 10956 (US). DOBRUSIN, Ellen, Myra [US/US]; 2205 Winchell, Ann Arbor, MI 48104 (US). DOHERTY, Annette, Marian [US/FR]; 8ème étage, 33, rue Poussin, F-75016 Paris (FR). FATTACY, Ali [IR/US]; Apartment 202, 1770 Green Street, San Francisco, CA 94123 (US). FRY, David, W. [US/US]; 4659 Ash Court, Ypsilanti, MI 48197 (US). BARVIAN, Mark, R. [US/US]; 1037 Morningside Drive, Ann Arbor, MI 48103 (US). KALLMEYER, Susanne, Trumpp [DE/US]; Apartment 92, 2735 Windwood Drive, Ann Arbor, MI 48105 (US). WU, Zhipei [CN/US]; 1436 Hidden Creek South, Saline, MI 48176 (US).</p>		<p>(74) Agents: RYAN, M. Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al. (81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. (88) Date of publication of the international search report: 5 November 1998 (05.11.98)</p>
<p>(54) Titre: PYRIDO[2,3-D]PYRIMIDINES AND 4-AMINO-PYRIMIDINES AS INHIBITORS OF CELL PROLIFERATION</p>		
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>(I)</p> </div> <div style="text-align: center;">  <p>(II)</p> </div> </div>		
<p>(57) Abstract</p> <p>This invention provides pyridopyrimidines and 4-aminopyrimidines that are useful for treating cell proliferative disorders, such as cancer and restenosis. We have now discovered a group of 7,8-dihydro-2-(amino and thio)pyrido[2,3-d]pyrimidines and 4-aminopyrimidines that are potent inhibitors of cyclin-dependent kinases (cdks) and growth factor-mediated kinases. The compounds are readily synthesized and can be administered by a variety of routes, including orally, and have sufficient bioavailability. This invention provides compounds of Formula (I) and Formula (II), where W is NH, S, SO, or SO₂, R¹ includes phenyl and substituted phenyl, R² includes alkyl and cycloalkyl, R³ includes alkyl and hydrogen, R⁸ and R⁹ include hydrogen and alkyl, and Z is carboxy. This invention also provides pharmaceutical formulations comprising a compound of Formula (I or II) together with a pharmaceutically acceptable carrier, diluent, or excipient therefor.</p>		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/01343

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D471/04 C07D401/04 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BORREL, J.I. ET AL.: "An unequivocal Synthesis of 4-amino-1,5,6,8-tetrahydropyrido[2,3-d]pyrimidine-2,7-diones and"</p> <p>COLL. CZECH. CHEM. COMMUN., vol. 61, no. 6, 1996, PRAGUE, pages 901-909, XP002069589</p> <p>* see pasge 902, ex. 6a, 6b *</p> <p>see the whole document</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/01343

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HURLBERT, B.S. ET AL.: "Studies on Condensed Pyrimidine Systems. XXIII. Synthesis of 2,4-Diaminopyrido'2,3-d!pyrimidines ..." J.MED.CHEM., vol. 11, 1968, WASHINGTON, pages 703-707, XP002069108 * see page 707, 6 table III * see the whole document	1
X	BAKER, B.R. ET AL.: "Analogues of Tetrahydrofolic acid. XIX. On the Mode of Binding of the Pyrimidyl Moiety ..." J.HETEROCYCLIC.CHEM., vol. 1, 1964, ALBUQUERQUE, pages 263-270, XP002069109 * see page 265, XIV, XV * see the whole document	1
X	ANDERSON ET AL.: "Pyridopyrimidines. 6. Nucleophilic Substitutions in the Pyrido'2,3-d!pyrimidine Series" J.ORG.CHEM., vol. 42, 1977, WASHINGTON, page 993 XP002069110 * see page 994, ex. 11 * see the whole document	1
X	SCHOFFSTALL, A.M. ET AL.: "Synthesis of 5,6-Dihydropyrido'2,3-d!pyrimidine Derivatives Directly from Acyclic Precursors " J.ORG.CHEM., vol. 36, no. 16, 1971, WASHINGTON, pages 2385-2387, XP002069111 see the whole document	1
X	VICTORY, P. ET AL.: "New Synthesis of pyrido'2,3-d!pyrimidines. 1. Reaction of 6-alkoxy-5-cyano-3,4-dihydro-2-pyridones with Guanidine and Cyanamide " HETEROCYCLES, vol. 23, no. 5, 1985, pages 1135-1141, XP002069590 * see page 1136, ex. 6a, 6b and formula 7 * see the whole document	1

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/01343

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VICTORY, P. ET AL.: "Cyclisation of Dinitriles by hydrogen halides. 1. Hydrogen bromide." HETEROCYCLES, vol. 23, no. 8, 1985, pages 1947-1950, XP002069591 * see page 1948, scheme 2, ex. 2, 4 * see the whole document ---	1
X	VICTORY, P. ET AL.: "Nueva síntesis de pirido'2,3-d!pirimidinas. V. Deshidrogenación del anillo dihidropiridonico" AFINIDAD, vol. 46, March 1989, pages 107-113, XP002069623 * see in particular page 109, table I, ex. 12 * see the whole document ---	1
X	WO 92 20642 A (RHONE-POULENC RORER INT) 26 November 1992 * see the definition of ArI and ArII together with n,m=0 and X=Z=NR' * see the whole document ---	1-26
Y	REWCASTLE G W ET AL: "TYROSINE KINASE INHIBITORS. 10. ISOMERIC 4-(3-BROMOPHENYL)AMINOPYRIDO D-PYRIMIDINES ARE POTENT ATP BINDING SITE INHIBITORS OF THE TYROSINE KINASE FUNCTION OF THE EPIDERMAL GROWTH FACTOR RECEPTOR" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 9, 1996, pages 1823-1835, XP002046257 see the whole document ---	1-26
Y	WO 96 34867 A (WARNER LAMBERT CO) 7 November 1996 see the whole document ---	1-19, 26
Y	WO 96 15128 A (WARNER LAMBERT CO) 23 May 1996 see the whole document ---	1-19, 26
Y	EP 0 021 292 A (WELLCOME FOUND) 7 January 1981 see the whole document ---	1-19, 26
Y	EP 0 278 686 A (WELLCOME FOUND) 17 August 1988 see the whole document ---	1-19, 26
5 Y	WO 95 09845 A (LILLY CO ELI) 13 April 1995 see the whole document ---	20-26
2	---	-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/01343

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 15952 A (ZENECA LTD ;THOMAS ANDREW PETER (GB)) 15 June 1995 see the whole document -----	20-26
P,X	WO 97 38992 A (SUMITOMO PHARMA) 23 October 1997 see the whole document -----	1-19, 26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/01343

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9220642 A	26-11-1992	AT 159009 T AU 658646 B AU 1993492 A CA 2102780 A DE 69222637 D DE 69222637 T DK 584222 T EP 0584222 A ES 2108120 T JP 6507643 T MX 9202181 A US 5409930 A US 5480883 A US 5710158 A US 5646153 A US 5721237 A US 5714493 A	15-10-1997 27-04-1995 30-12-1992 11-11-1992 13-11-1997 26-02-1998 23-02-1998 02-03-1994 16-12-1997 01-09-1994 01-05-1993 25-04-1995 02-01-1996 20-01-1998 08-07-1997 24-02-1998 03-02-1998
WO 9634867 A	07-11-1996	US 5620981 A US 5733914 A AU 5576996 A CA 2214219 A CZ 9703275 A EP 0823908 A NO 975033 A PL 323089 A	15-04-1997 31-03-1998 21-11-1996 07-11-1996 18-03-1998 18-02-1998 31-10-1997 02-03-1998
WO 9615128 A	23-05-1996	US 5733913 A AU 4107896 A CZ 9701390 A EP 0790997 A FI 971953 A HU 76853 A NO 972198 A PL 320169 A ZA 9509675 A CA 2199964 A	31-03-1998 06-06-1996 18-02-1998 27-08-1997 12-05-1997 29-12-1997 13-05-1997 15-09-1997 29-05-1996 23-05-1996
EP 0021292 A	07-01-1981	AU 5927580 A CA 1132137 A	18-12-1980 21-09-1982

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/01343

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0021292 A		DK 254780 A,B, FI 801912 A,B, JP 1456317 C JP 56018982 A JP 63004539 B US 4897395 A US 4372957 A US 4661490 A ZA 8003539 A US 4959474 A	15-12-1980 15-12-1980 09-09-1988 23-02-1981 29-01-1988 30-01-1990 08-02-1983 28-04-1987 27-01-1982 25-09-1990
EP 0278686 A	17-08-1988	AU 598093 B AU 1135688 A JP 63216885 A	14-06-1990 11-08-1988 09-09-1988
WO 9509845 A	13-04-1995	US 5426110 A AU 7930394 A CA 2173234 A EP 0722440 A JP 9503509 T	20-06-1995 01-05-1995 13-04-1995 24-07-1996 08-04-1997
WO 9515952 A	15-06-1995	AU 1194895 A EP 0733045 A JP 9506363 T ZA 9409546 A	27-06-1995 25-09-1996 24-06-1997 23-06-1995
WO 9738992 A	23-10-1997	AU 2521597 A	07-11-1997